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Copper-/Silver-Mediated Arylation of C(sp^2)−H Bonds with 2-Thiophenecarboxylic Acids

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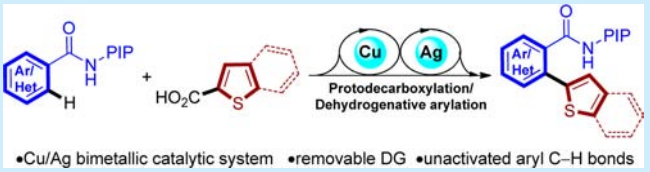
Supporting Information

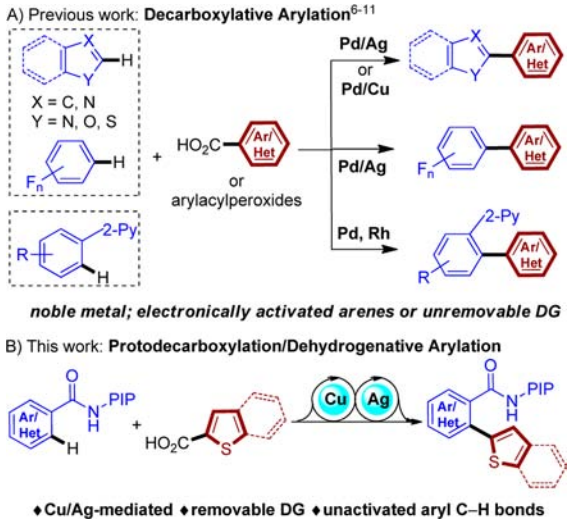
ABSTRACT: A copper/silver-mediated arylation of (hetero)-aryl C−H bonds with 2-thiophenecarboxylic acids has been achieved. The protocol features a broad substrate scope and high functional group tolerance. Preliminary mechanistic studies indicate that a cascade protodecarboxylation/dehydrogenative coupling process is likely involved.



Transition-metal-catalyzed decarboxylative arylation has emerged as one of the most powerful and versatile strategies for the synthesis of biaryl compounds.[1] Compared to the use of toxic and expensive organometallics as aryl source in traditional cross-coupling reactions, this strategy employs readily available, inexpensive, and nontoxic aromatic carboxylic acids as coupling partners and generates gaseous CO_2 instead of toxic metal salts as waste. Since the pioneering work of Myers and Gooßen, decarboxylative coupling of benzoic acids with aryl halides or triflates using Pd/Cu or Pd/Ag bimetallic catalyst systems have been extensively studied.[2] In 2009, the Liu group reported the first example of copper-catalyzed decarboxylative coupling of potassium polyfluorobenzoates with aryl iodides and bromides.[3]

Recently, transition-metal-catalyzed decarboxylative C−H arylation has demonstrated great potential in biaryl synthesis by taking advantage of both the high efficiency of C−H activation and the diversity of carboxylic acids.[4−12] For example, the groups of Crabtree and Glorius first demonstrated the synthetic potential of the tandem decarboxylation/C−H activation process.[4,5] Subsequently, Larrosa,[6] Su,[7] Greaney,[8] and others[9] demonstrated the palladium-catalyzed decarboxylative arylation of activated heteroarenes, such as indoles, thiophenes, azoles, and polyfluoroarenes (Scheme 1A). Despite significant progress in this area, these established methods have been limited to activated or electronically biased arenes, such as highly C−H acidic polyfluoroarenes or azoles and electron-rich indoles or thiophenes. To achieve decarboxylative arylation of C(sp^2)−H bonds, preinstalled directing groups have been found to be promising. Yu and Chan reported a Pd-catalyzed decarboxylative arylation of 2-arylpyridines using arylacylperoxides as aryl sources.[10] Recently, Shi developed a rhodium-catalyzed decarbonylative arylation of simple aryl C−H bonds of 2-arylpyridines with aromatic carboxylic acids (Scheme 1B).[11] However, the use of unremovable directing group, and the need for the reactions to be conducted at high temperature (140 °C) restrict the application of this protocol. Moreover, the reported methods commonly rely on the use of precious transition metals, such as Pd/Ag and Pd/Cu bimetallic catalytic systems, or rhodium catalyst.

Scheme 1. Transition-Metal-Catalyzed C−H Arylation with Aromatic Carboxylic Acids as Aryl Source

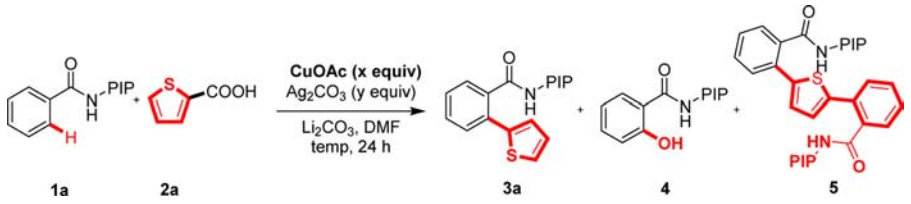


Recently, the elegant work by Liu has shown that the decarboxylative coupling of potassium polyfluorobenzoates with aryl iodides and bromides could be catalyzed by copper only.[3a] As part of our ongoing research on the use of our newly developed bidentate directing group derived from (pyridin-2-yl)isopropyl amine (PIP-amine) for copper-catalyzed/mediated C−H functionalization reactions,[13−15] we report here the arylation of (hetero)aryl C−H bonds with 2-thiophenecarboxylic acids mediated by a Cu/Ag bimetallic catalyst system via a hypothetic protodecarboxylation/dehydrogenative coupling sequence (Scheme 1B). It is noteworthy that this protocol represents the first example of protodecarboxylation/dehydro-

Received: May 28, 2015
Published: June 23, 2015

DOI: 10.1021/acs.orglett.5b01560
Org. Lett. 2015, 17, 3338−3341

Table 1. Optimization of the Reaction Conditions[a]



entry	[Cu] (equiv)	[Ag] (equiv)	Li_2CO_3 (equiv)	temp (°C)	DMF (mL)	yield[b] (%) 3a (mono:di)	4	5
1	1.0	Ag_2CO_3 (3.0)		120	1.5	43 (9.8:1)[d]	13	16
2	0.8	Ag_2CO_3 (3.0)		120	1.5	56 (8.3:1)	11	19
3	0.2	Ag_2CO_3 (3.0)		120	1.5	49 (8.8:1)	5	24
4	0.2	Ag_2CO_3 (3.0)	3.0	120	1.5	40 (19:1)	N.D.	6
5	0.2	$AgNO_3$ (4.0)	3.0	120	1.5	68 (10.3:1)	N.D.	14
6	0.4	$AgNO_3$ (4.0)	3.0	110	3.0	73 (11.2:1)[d]	1	10
7	0.4	$AgNO_3$ (4.0)	3.0	100	3.0	80 (9:1)[d]	4	8
8[c]	**0.4**	**$AgNO_3$ (4.0)**	**5.0**	**100**	**3.0**	**93 (6.8:1)**[d]	**2**	**3**
9[c]		$AgNO_3$ (4.0)	5.0	100	3.0	N.D.	N.D.	N.D.

[a]Reaction conditions: **1a** (0.15 mmol), CuOAc (*x* equiv), [Ag] (*y* equiv), **2a** (3 equiv), and Li_2CO_3 (*z* equiv) in DMF for 24 h. [b]^{1}H NMR yield using CH_2Br_2 as the internal standard. [c]**2a** (5 equiv). [d]Isolated yield.

genative C−H arylation catalyzed by the inexpensive and abundant copper catalyst.[16,17]

During the screening of reaction conditions for Cu-mediated hydroxylation,[13b] we surprisingly obtained a trace amount of the arylated product **3a** when CuTc was used as catalyst. We hypothesized that this may result from the decarboxylative arylation of benzamide **1a**. Therefore, we commenced to investigate this reaction and were delighted to find that the desired arylation product **3a** can be obtained in moderate yield in the presence of various copper salts and Ag_2CO_3. Surprisingly, CuOAc was found to be the optimal catalyst and gave **3a** in 43% yield, probably via in situ generation of Cu(II) species by the oxidation of silver carbonate (Table 1, entry 1). The catalyst loading could be reduced to 0.2 equiv without significantly affecting the yield (entries 2 and 3). The addition of Li_2CO_3 increased both the yield and the selectivity of **3a** and avoided the unwanted byproducts **4** and **5** (entry 4). The screening of silver salts showed that $AgNO_3$ could dramatically increase the yield to 68% (entry 5, mono:di = 10:1). To our delight, simply tuning the concentration of the reaction, increasing the loading of Li_2CO_3, and lowering the reaction temperature to 100 °C could dramatically inhibit the unwanted side reactions and enhance the desired reaction (entries 6−8, for more extensive screening, see Tables S2−S10).[18] A control experiment indicated that copper was crucial for this reaction (entry 9). We also found that the PIP-directing group is essential for this transformation. The use of 8-aminoquinoline as directing group only resulted in the formation of hydroxylation product with no trace of arylated product (Scheme S2).[18]

With the optimized reaction conditions in hand, we first tested the substrate scope of different benzamides **1**. As shown in Figure 1, both electron-donating and electron-withdrawing benzamides were well tolerated, and moderate to good yields of the corresponding substituted 2-(thiophene-2-yl)benzamides **3a−m** were obtained. A broad range of functional groups, such as fluoro (**3b** and **3f**), chloro (**3c** and **3i**), methoxy (**3d** and **3m**), bromo (**3g**), trifluoromethyl (**3h**), methoxycarbonyl (**3j**), and acetyl (**3l**), were compatible with this protocol. Notably, *meta*-methylbenzamide **1e** gave arylated product exclusively at

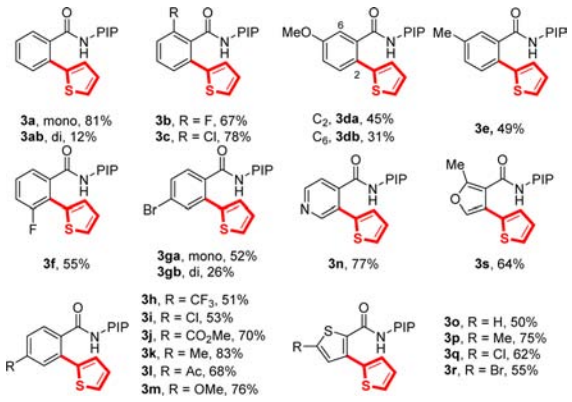


Figure 1. Scope of benzamides. Reaction conditions: **1** (0.15 mmol), $AgNO_3$ (4 equiv), CuOAc (0.4 equiv), **2a** (5 equiv), and Li_2CO_3 (5 equiv) in DMF (3 mL) at 100 °C, 24 h. Isolated yield.

the 6-position, owing to the steric interactions. On the contrary, *m*-methoxybenzamide **1d** gave a mixture of the arylated products at both the 2- and 6-positions (**3da** and **3db**), probably due to the coordinating effect of the alkoxy substituent. *m*-Fluorobenzamide **3f** exclusively led to the arylation at the kinetically more acidic C-2 position.[19] It is noteworthy that the heterocyclic substrates, such as isonicotinamide **3n** and various substituted thiophene-2-PIP-carboxamides **3o−s** were all tolerated under the reaction conditions, providing an expeditious access to biologically important (hetero)biaryl compounds. Unfortunately, the reaction does not work with furancarboxylic acids under the optimized conditions.

We then examined the substrate scope of various heteroaromatic carboxylic acids (Figure 2). Generally, functionalized thiophene-2-carboxylic acids, 2,5-dichlorothiophene-3-carboxylic acid, and benzothiophene-2-carboxylic acid were all suitable substrates, furnishing the desired products in good yields (41%−84%). The halogen substituents (**4b**, **4d**, **4h**) were compatible with this reaction.

The decarboxylative arylation reaction could be conducted on gram scale, and the desired product **3a** was obtained in 90%

DOI: 10.1021/acs.orglett.5b01560
Org. Lett. 2015, 17, 3338−3341

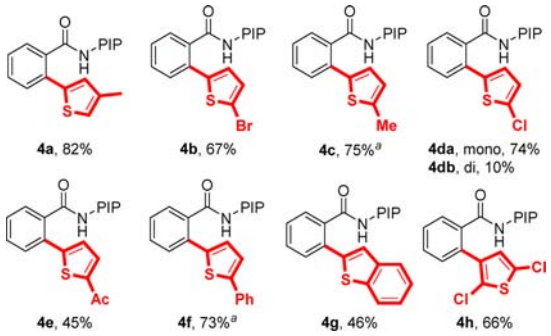
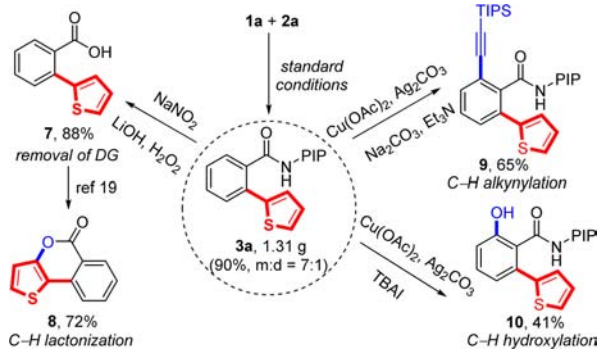


Figure 2. Scope of carboxylic acids. Reaction conditions: **1a** (0.15 mmol), $AgNO_3$ (4 equiv), CuOAc (0.4 equiv), **2** (5 equiv), and Li_2CO_3 (5 equiv) in DMF (3 mL) at 100 °C, 24 h. Isolated yield. Note a: Ag_2CO_3 was used instead of $AgNO_3$.

yield (Scheme 2, 1.31 g). Furthermore, the PIP group of compound **3a** can be readily removed in 88% yield via a

Scheme 2. Gram-Scale Synthesis and Removal of the Directing Group

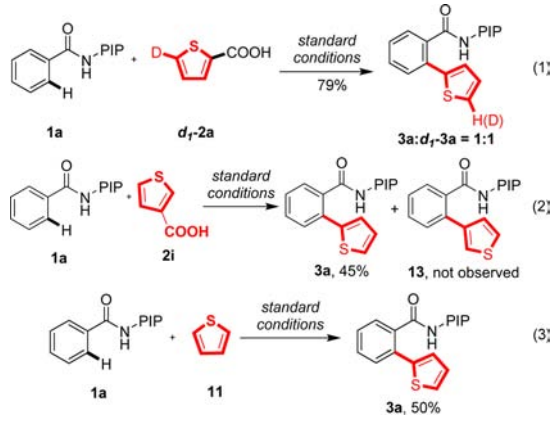


nitrosylation/hydrolysis sequence, affording 2-(thiophene-2-yl)benzoic acid **7** in 88% yield.[13a] Compound **7** can be transferred to the corresponding biaryl lactone **8** in 72% yield as reported by Wang.[20]

The synthetic versatility of this protocol can be further demonstrated by a set of PIP-directed sequential C−H functionalization reactions developed by our group recently (Scheme 2). For example, the decarboxylative C−H arylation product **3a** can undergo copper-mediated C−H alkynylation to give the 2-(thiophene-2-yl)-6-((triisopropylsilyl)ethynyl)-benzamide **9** in 65% yield.[13] Similarly, copper-mediated C−H hydroxylation of **3a** using our previous established conditions provided 2-hydroxy-6-(thiophen-2-yl)benzamide **10** in 41% yield.[13d]

To gain further insight into the course of the reaction, we conducted a series of competition and radical-trapping experiments.[18] The intermolecular KIE for decarboxylative C−H arylation is 3.0, while the intramolecular KIE is 2.3. These data suggest that C−H cleavage is either the turnover-limiting step or the turnover-limiting step occurs prior to C−H cleavage. Addition of 1 equiv of radical scavengers, such as 1,4-dinitrobenzene and 1,1-diphenylethylene, did not inhibit the reaction. Addition of 1 equiv of TEMPO substantially reduced the yield but still did not completely suppress the reaction. These observations suggest that the transformation does not proceed via radical intermediates.

To verify whether the reaction proceeded via decarboxylative arylation or a protodecarboxylation/dehydrogenative arylation sequence, we conducted additional experiments. The reaction of **1a** with 5-deuterated 2-thiophenecarboxylic acid (d_1-**2a**) gave the products **3a** and d_1-**3a** in a 1:1 ratio (eq 1). When 3-



thiophenecarboxylic acid **2i** was used under the standard conditions, **3a** was obtained as the sole product and no **13** was observed (eq 2). In addition, the reaction of **1a** with thiophene **11** under the standard conditions was conducted, affording **3a** in 50% yield (eq 3). These results indicated that thiophene might be formed in situ through the protodecarboxylation, and subsequent dehydrogenative arylation afforded the desired product.[21,22]

In conclusion, we have developed the first copper-catalyzed arylation of C(sp^2)−H bonds with 2-thiophenecarboxylic acids as aryl source. This reaction is scalable and tolerates a wide range of functional groups, providing a valuable synthetic entry to biaryl compounds. Preliminary mechanistic studies reveal that a cascade protodecarboxylation/dehydrogenative arylation process is probably involved.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01560.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Basic Research Program of China (2015CB856600) and the NSFC (21422206, 21272206) is gratefully acknowledged.

■ REFERENCES

(1) For reviews, see: (a) Baudoin, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 1373. (b) Shang, R.; Liu, L. *Sci. China Chem.* **2011**, *54*, 1670. (c) Gooßen, L. J.; Rodríguez, N.; Gooßen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100. (d) Rodríguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030. (e) Cornella, J.; Larrosa, I. *Synthesis* **2012**, *5*, 653.

(2) For early examples, see: (a) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250. (b) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323. (c) Gooßen, L. J.;

DOI: 10.1021/acs.orglett.5b01560
Org. Lett. 2015, 17, 3338−3341

Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662. (d) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350. (e) Becht, J.-M.; Catala, C.; Drian, C. L.; Wagner, A. *Org. Lett.* **2007**, *9*, 1781.

(3) (a) Shang, R.; Fu, Y.; Wang, Y.; Xu, Q.; Yu, H.-Z.; Liu, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 9350. (b) Jia, W.; Jiao, N. *Org. Lett.* **2010**, *12*, 2000.

(4) Voutchkova, A.; Coplin, A.; Leadbeater, N. E.; Crabtree, R. H. *Chem. Commun.* **2008**, 6312.

(5) (a) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194. (b) Wang, C.; Rakshit, S.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 14006.

(6) Cornella, L.; Lu, P.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506.

(7) (a) Zhou, J.; Hu, P.; Zhang, M.; Huang, S.; Wang, M.; Su, W. *Chem.—Eur. J.* **2010**, *16*, 5876. (b) Zhao, H.; Wei, Y.; Xu, J.; Kan, J.; Su, W.; Hong, M. *J. Org. Chem.* **2011**, *76*, 882. (c) Hu, P.; Zhang, M.; Jie, X.; Su, W. *Angew. Chem.* **2012**, *124*, 231; *Angew. Chem., Int. Ed.* **2012**, *51*, 227. (d) Pei, K.; Jie, X.; Zhao, H.; Su, W. *Eur. J. Org. Chem.* **2014**, 4230.

(8) Zhang, F.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 2768.

(9) (a) Xie, K.; Yang, Z.; Zhou, X.; Li, X.; Wang, S.; Tan, Z.; An, X.; Guo, C.-C. *Org. Lett.* **2010**, *12*, 1564. (b) Luo, H.-Q.; Dong, W.; Loh, T.-P. *Tetrahedron Lett.* **2013**, *54*, 2833.

(10) Yu, W.-Y.; Sit, W. N.; Zhou, Z.; Chan, A. S.-C. *Org. Lett.* **2009**, *11*, 3174.

(11) Pan, F.; Lei, Z.-Q.; Wang, H.; Li, H.; Sun, J.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2013**, *52*, 2063.

(12) For decarbonylative couplings, see: (a) Zhao, X.; Yu, Z. *J. Am. Chem. Soc.* **2008**, *130*, 8136. (b) Jin, W.; Yu, Z.; He, W.; Ye, W.; Xiao, W.-J. *Org. Lett.* **2009**, *11*, 1317. (c) Shuai, Q.; Yang, L.; Guo, X.; Baslé, O.; Li, C.-J. *J. Am. Chem. Soc.* **2010**, *132*, 12212. (d) Amaike, K.; Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 13573. (e) Lu, Q.; Yu, H.; Fu, Y. *J. Am. Chem. Soc.* **2014**, *136*, 8252.

(13) (a) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 4187. (b) Li, X.; Liu, Y.-H.; Gu, W.-J.; Li, B.; Chen, F.-J.; Shi, B.-F. *Org. Lett.* **2014**, *16*, 3904. (c) Chen, F.-J.; Liao, G.; Li, X.; Wu, J.; Shi, B.-F. *Org. Lett.* **2014**, *16*, 5644. (d) Yin, X.-S.; Li, Y.-C.; Yuan, J.; Gu, W.-J.; Shi, B.-F. *Org. Chem. Front.* **2015**, *2*, 119. (e) Li, B.; Liu, B.; Shi, B.-F. *Chem. Commun.* **2015**, *51*, 5093.

(14) For pioneering work on the use of a bidentate auxiliary, see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (c) For a recent review, see: Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (d) Zhang, B.; Guan, H.-X.; Liu, B.; Shi, B.-F. *Chin. J. Org. Chem.* **2014**, *34*, 1487. (e) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1063. (f) Rit, R. K.; Yadav, R.; Ghosh, K.; Sahoo, A. K. *Tetrahedron* **2015**, *71*, 4450.

(15) For examples of Cu-mediated C−H functionalization directed by bidentate auxiliary, see: (a) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237. (b) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342. (c) Roane, J.; Daugulis, O. *Org. Lett.* **2013**, *15*, 5842. (d) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4457. (e) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 9797. (f) Urones, B.; Martínez, Á. M.; Rodríguez; Arrayάs, R. G.; Carretero, J. *Chem. Commun.* **2013**, *49*, 11044. (g) Wang, Z.; Ni, J.-Z.; Kuninobu, Y.; Kanai, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 3496. (h) Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 3354.

(16) For selected reviews and early examples of copper-catalyzed C−H activation, see: (a) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464. (b) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062. (c) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (d) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (e) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842. (f) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (g) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411. (h) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593.

(17) Yu, L.; Li, P.; Wang, L. *Chem. Commun.* **2013**, *49*, 2368 and references therein.

(18) See the Supporting Information.

(19) Song, W.; Ackermann, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 8251.

(20) (a) Li, Y.; Ding, Y.-J.; Wang, J.-Y.; Su, Y.-M.; Wang, X.-S. *Org. Lett.* **2013**, *15*, 2574. (b) Gallardo-Donaire, J.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 9350.

(21) For selected examples of dehydrogenative cross-coupling, see: (a) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (b) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (c) Dong, J.; Long, Z.; Song, F.; Wu, N.; Guo, Q.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 580. (d) Chen, X.; Dobereiner, G.; Hao, X.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Tetrahedron* **2009**, *65*, 3085. (e) Grigorjeva, L.; Daugulis, O. *Org. Lett.* **2015**, *17*, 1204. (f) Kitahara, M.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2011**, *133*, 2160. (g) Odani, R.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10784.

(22) At this stage, a reaction pathway involved the combination of decarboxylatve C−H arylation and protodecarboxylation/dehydrogenative arylation could not be excluded.

DOI: 10.1021/acs.orglett.5b01560
Org. Lett. 2015, 17, 3338−3341